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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,913	12/31/2001	Ulf Landegren	LAND DIV	5983

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/029,913	Landegren
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Oct 21, 2003* .

2a) [ ] This action is **FINAL**. 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-13* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-13* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [X] Other: *Detailed Action*

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 21, 2003 has been entered. Claim 1 has been amended. Currently claims 1-13 are pending in this application.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CAR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1 and 5-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 5,871,921 (February 16, 1999) . Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-46 of U.S. Patent No. 5,871,921 disclose the basic and fundamental method of instant claims of detecting target nucleic acid sequence in a sample by a) hybridizing the target sequence to the probe ends under hybridizing conditions; b) covalently connecting the ends of the hybridized probe with each other to form a circularized structure; c) cleaving the cleavable function; d) separating the detectable functions no longer linked to the solid phase; and e) detecting the presence and, if desired, location of the remaining probe as indicative of the presence of the target nucleic acid sequences. Moreover, U.S. Patent No. 5,871,921 also discloses the quantification and distinguishing between sequence variants with regards to one or several target sequences in a sample (Column 6, lines 2-3). It would have been *prima facie* obvious to an ordinary practitioner to combine the teaching of quantification and distinguishing between sequence variants with regards to one or several target sequences in a sample in the

specification with the claims 1-46 of U.S. Patent No. 5,871,921 to invent the instantly claimed method.

4. Claims 2-4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 5,871,921 in view of Urdea et al. (U.S. Patent 5,124,246) (23 June, 1992).

Claims 1-46 of U.S. Patent No. 5,871,921 teach the methods of Claims 1, and 5-13 as described above.

Claims 1-46 of U.S. Patent No. 5,871,921 do not teach the detectable function is cleavable by cleaving a cleavable linker located on the same probe end as the detectable function.

Urdea et al. teach the detectable function is cleavable by cleaving a cleavable linker located on the same probe end as the detectable function (Figures 3-2 and Column 12, lines 49 to column 13, line 43).

Claims 1-46 of U.S. Patent No. 5,871,921 do not teach the branched or bifurcated probes.

Urdea et al. teaches a circularizable probe comprising two free cleavable or detectable nucleic acid end parts which are linear, branched or bifurcated and are capable of hybridizing to two at least substantially neighboring regions of a target sequence (abstract, examples 1, 2 and 3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the branched or bifurcated probes of Urdea et al. in the method of Claims 1-46 of U.S. Patent No. 5,871,921 since Urdea et al state, "Suitable cleavable linker molecules may be incorporated into the multimers at predetermined sites for the purpose of

analyzing the structure of the multimer or as a means for releasing predetermined segments (such as the portion of the multimer that binds to the oligonucleotide) (Column 12, lines 49-55)". Moreover, Urdea et al. states " The multimers may be used in essentially any of the known nucleic acid hybridization formats, such as those in which the analyte is bound directly to a solid phase or sandwich hybridization in which the analyte is bound to an oligonucleotide that is in turn bound to a solid phase (Column 13, lines 56-61)". An ordinary practitioner would have been motivated to combine and substitute the branched or bifurcated probes of Urdea et al. into the method of Claims 1-46 of U.S. Patent No. 5,871,921 in order to achieve the express advantages, as noted by Urdea et al., to improve the sensitivity of nucleic acid based assay by applying multimers, which may be used in essentially any of the known nucleic acid hybridization formats, such as those in which the analyte is bound directly to a solid phase or sandwich hybridization in which the analyte is bound to an oligonucleotide that is in turn bound to a solid phase.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 5, 6 and 9-13 are rejected under 35 U.S.C. 103(a) as being obvious over Nilsson et al (Science, Vol. 265, pages 2085-2088) (30 September, 1994) in view of Fildes et al. (U.S. Patent 5,643,724) (July 1, 1997)..

With regard to claim 1 in the 103(a) rejection, a cleavable, detectable function is broadly interpreted to include any removable detectable thing. For example, a nucleotide can be exonuclease treated and detected. Alternately, a biotin label could be chemically removed. Nilsson et al. teaches a method of detecting a target nucleic acid sequence in a sample by contacting the sample with a detectable probe to hybridize the probe to the target sequence, and detecting the hybridized probe, said probe having two free nucleic acid end parts which are at least partially complementary to and capable of hybridizing to two at least substantially neighboring regions of the target sequence (Figure 4), comprising the following steps:

a) hybridizing the probe ends to the target sequence under hybridization conditions (Figure 4);

b) covalently connecting the ends of the hybridized probe with each other to form a circularizable structure (Figure 4).

c) cleaving the cleavable function (i.e.,washing under denaturing conditions in this case) (Figure 4);

characterized in that the probe is provided with a cleavable or dissociable detectable function (Figure 4), and the method comprising the further steps of:

d) separating detectable functions no longer linked to the solid phase (Figure 4);

e) detecting the presence and, if desired, location of the remaining probe as indicative of the presence of the target nucleic acid sequence (Figure 4).

Nilsson et al. teaches that the detectable function is dissociable by being provided either on a further circularizable probe or on a target-specific probe (Figure 4).

Nilsson et al. further teaches the performance covalent connection of the probe ends by enzymatic or chemical ligation (Figure 4).

Nilsson et al. teaches the DNA or RNA as target molecule (Figure 4).

Nilsson et al. teaches the immobilization of oligonucleotide probes as well as the target sequence to a solid phase (Figure 4).

Nilsson et al do not teach the method of quantifying, and distinguishing between sequence variants with regards to one or several target sequences in a sample.

Fildes et al. teach the method of quantifying, and distinguishing between sequence variants with regards to one or several target sequences in a sample (Abstract, Column 6, lines 5-21, Column 8, line 61 to Column 9, line 10, and claims 1, 6, 11, and 14).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the method of quantifying, and distinguishing between sequence variants with regards to one or several target sequences in a sample of Fildes et al in the method of Nilsson et al. since Fildes et al state, "This typing facilitates typing tissue for determining individual identity and has application in the field of forensic science (Abstract, last sentence)". Moreover, Fildes et al. states " The alleles can be detected and distinguished using sequence-specific oligonucleotide probes (Column 6, lines 5-6)".An ordinary practitioner would have been motivated to substitute and combine the method of quantifying, and distinguishing

between sequence variants with regards to one or several target sequences in a sample of Fildes et al. in the method of Nilsson et al. in order to achieve the express advantages, as noted by Fildes et al., of an invention by which alleles can be detected and distinguished using sequence-specific oligonucleotide probes.

7. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al (Science, Vol. 265, pages 2085-2088) (30 September, 1994) in view of Fildes et al. (U.S. Patent 5,643,724) (July 1, 1997) further in view of Urdea et al. (U.S. Patent 5,124,246) (23 June, 1992).

Nilsson et al. in view of Fildes et al. teach the methods of Claims 1, 5, 6 and 9-13 as described above.

Nilsson et al. in view of Fildes et al. do not teach the detectable function is cleavable by cleaving a cleavable linker located on the same probe end as the detectable function.

Urdea et al. teach the detectable function is cleavable by cleaving a cleavable linker located on the same probe end as the detectable function (Figures 3-2 and Column 12, lines 49 to column 13, line 43).

Nilsson et al. in view of Fildes et al. do not teach the branched or bifurcated probes.

Urdea et al. teaches a circularizable probe comprising two free cleavable or detectable nucleic acid end parts which are linear, branched or bifurcated and are capable of hybridizing to two at least substantially neighboring regions of a target sequence (abstract, examples 1, 2 and 3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time

the invention was made to substitute the branched or bifurcated probes of Urdea et al. in the method of Nilsson et al. in view of Fildes et al. since Urdea et al state, "Suitable cleavable linker molecules may be incorporated into the multimers at predetermined sites for the purpose of analyzing the structure of the multimer or as a means for releasing predetermined segments (such as the portion of the multimer that binds to the oligonucleotide) (Column 12, lines 49-55)". Moreover, Urdea et al. states " The multimers may be used in essentially any of the known nucleic acid hybridization formats, such as those in which the analyte is bound directly to a solid phase or sandwich hybridization in which the analyte is bound to an oligonucleotide that is in turn bound to a solid phase (Column 13, lines 56-61)". An ordinary practitioner would have been motivated to combine and substitute the branched or bifurcated probes of Urdea et al. into the method of Nilsson et al. in view of Fildes et al. in order to achieve the express advantages, as noted by Urdea et al., to improve the sensitivity of nucleic acid based assay by applying multimers, which may be used in essentially any of the known nucleic acid hybridization formats, such as those in which the analyte is bound directly to a solid phase or sandwich hybridization in which the analyte is bound to an oligonucleotide that is in turn bound to a solid phase..

8. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al (Science, Vol. 265, pages 2085-2088) (30 September, 1994) in view of Fildes et al. (U.S. Patent 5,643,724) (July 1, 1997) further in view of Birkenmeyer et al. (U.S. Patent 5,427,930) (27 June, 1995).

Nilsson et al. in view of Fildes et al. teach the methods of Claims 1, 5, 6 and 9-13 as described above.

Nilsson et al. in view of Fildes et al. do not teach the interspace between probe ends which is filled by an extension reaction prior to covalently interconnecting the probe ends.

Birkenmeyer et al. teaches the interspace between probe ends which is filled by an extension reaction prior to covalently interconnecting the probe ends (abstract and example 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute gap filling ligase chain reaction in the method of Nilsson et al. in view of Fildes et al. since Birkenmeyer et al. states "It is therefore a primary object of the present invention to improve the sensitivity of nucleic acid based assay by decreasing the occurrence of target independent ligation which causes falsely positive background signal. This object is met in the present invention by modifying at least one probe end so that when hybridized with its complementary probe, the resulting duplex is not "blunt-ended" (i.e. ligatable) with respect to the partner complementary probe duplexes. After hybridization to the target, the modified ends are "corrected" in a target dependent fashion to render the adjacent probes ligatable. Several features of the probes and the associated target sequences taught in this application makes this task particularly elegant (column 2, lines 28-42)".An ordinary practitioner would have been motivated to combine gap filling ligase chain reaction into the method of Nilsson et al. in view of Fildes et al. in order to achieve the express advantages, as noted by

Birkenmeyer et al., to improve the sensitivity of nucleic acid based assay by decreasing the occurrence of target independent ligation.

Response to Amendment

9. In response to amendment, all previous 102(b) and 103(a) rejections are hereby withdrawn. However, new double patenting and 103 rejections are hereby included.

Response to Arguments

10. Applicant's arguments with respect to all pending claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. Any inquiry of a general nature or relating to the status of this application should be directed to the Group LIE Chantae Dessau, whose telephone number is (703) 605-1237. Papers related to this application may be submitted to

Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 is 703-872-9306. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Kr. Chakrabarti

ARUN K. CHAKRABARTI
PATENT EXAMINER

Arun Chakrabarti

Patent Examiner

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October 30, 2003

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